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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,055	05/11/2006	Jun Mori	128006	1488

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
04/19/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

OfficeAction25944@oliff.com
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Office Action Summary	Application No.	Applicant(s)	
	10/579,055	MORI ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 16-20* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 2/4/2010, are acknowledged and entered. Claims 12-15 have been cancelled by Applicant. Claims 16-20 are newly added. Claims 1-10 remain withdrawn from consideration. Claims 11 and 16-20 are presently under examination.

Response to Arguments

Applicants' arguments, filed 2/4/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicants argue that the submitted Declaration (Mori Declaration) describes Declarant's efforts to produce the skin patch according to Example 6 of Sugita. The Declaration indicates that preparation prepared according to Example 6 of Sugita came out in the form of the liquid with no viscosity and could no be spread on a non-woven polyester support. Applicant asserts that the Declaration provides evidence that patches as taught in Sugita cannot be suitably made with the active agent taught by Hiroyoshi.

Applicant's arguments and the Declaration of Mr. Mori have been fully and carefully considered but are not persuasive.

Firstly, Applicant's attention is directed to Sugita *et al.*, who teach that percutaneously administrable preparations of the invention include ointments, creams, solutions, gels, liniments, lotions, tapes, poultices, and patches, which can be prepared by known methods (col. 7, lines 57-60). The inventors teach that "at first" 1-menthol, lower alcohol, and phosphate buffer, water or isopropyl myristate are uniformly mixed (col. 7, lines 61-63) and then a cerebral function activator is added to the mixture, which is then exposed to ultrasonic waves (col. 7, lines 64-67). Then, the preparation is prepared in a "suitable method" according to the type of the form such as ointments, patches, or the like (col. 8, lines 1-3). Sugita *et al.* then provide a list of additives

"which are generally used for percutaneously administrable preparations", such as vehicles, antiseptics, stabilizers, pH regulators, surfactants, moisturizers, antioxidants, suspending agents, softeners, tackifiers, coloring agents, and a flavor (col. 8, lines 3-18). In a preferred embodiment, the mixture of active agent and base is mixed with a tackifier and the "then obtained paste-like mixture" is spread on the support (col. 8, lines 19-26).

Example 6 of Sugita discloses preparation of "patchs", which were prepared in a similar method to Example 5, which discloses preparation of poultices. The amount of active ingredient in Sugita was 1% (10 mg in 990 mg of aqueous base). In Declarant's preparation according to Sugita, wherein the claimed active agent is added to the aqueous base of Sugita, the percent active ingredient was 19.5%. Thus, Declarant is comparing different amounts of active agent and is not making a comparison only between different actives, but also different amounts of active agent. The Examiner is therefore not persuaded by Applicant's argument that patches as taught in Sugita cannot be suitably made with the active agent taught by Hiroyoshi.

Secondly, when comparing a preparation of the instant claims to those in Sugita, Declarant prepares a composition comprising 24.5% water, 5% isopropanol, and **35%** glycerin. The compositions in Sugita comprised 30% ethanol, 67% phosphate buffer, and **5%** glycerin. One skilled in the art would not expect a composition comprising 35% glycerin and 24.5% water to exhibit the same physical properties (*e.g.*, tackiness, viscosity, etc.) as a composition comprising 67% phosphate buffer and 5% glycerin.

Thirdly, the claims are not limited to the specific formulation prepared in the Mori Declaration. The claims encompass compositions comprising 1-20% by mass of a water-soluble polymer, 0.01 to 20% by mass of any cross-linking agent, 10 to 80% by mass of any polyhydric alcohol, and 1 to 80% by mass of water. The preparation in the Mori Declaration comprised specific amounts of active agent and specific amounts of specific water-soluble polymer (6% starch acrylate), cross-linking agent (0.2% aluminum hydroxide), polyhydric alcohol (35% glycerin), and water (24.6%). In addition, the preparations of the Mori Declaration comprise numerous excipients not recited in the instant claims (*e.g.*, talc, lactic acid, polysorbate 80, 1-menthol, etc.).

Sugita *et al.* disclose percutaneously absorbable preparations composed of an aqueous base comprising a cerebral function activator, 1-menthol, lower alcohol, and phosphate buffer

(col. 7, lines 61-67). The preparation is then prepared in a suitable method to the type of the form desired such as ointments or patches by addition of additives "generally used" for percutaneously administrable preparation. Such additives include vehicles (*e.g.*, vaseline, PEG 400, PEG 4000), stabilizers (*e.g.*, calcium hydroxide), pH regulators (*e.g.*, tartaric acid), surfactants (*e.g.*, sorbitan monooleate), moisturizers (*e.g.*, glycerin, propylene glycol), tackifiers (*e.g.*, glycerin, acrylic polymer) (col. 8, lines 1-18).

Koide *et al*. disclose tacky adhesive compositions comprising a drug, water-soluble polymer, cross-linking agent, polyhydric alcohol, and water. One skilled in the art would thus have been motivated to make and use tacky adhesive compositions as disclosed in Koide *et al*. to provide a means for percutaneously administering cerebral function activators as disclosed in Hiroyoshi and Sugita.

Accordingly, the Examiner is not persuaded that Applicant has demonstrated that the percutaneously administrable preparations disclosed in Sugita are not "suitable" for use with the claimed active agent.

Declaration under Rule 1.132

The Examiner acknowledges receipt of the Rule 1.132 Declaration of Mori ("Mori" Declaration) and has carefully considered the information provided therein.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Hiroyoshi *et al.*** (Japanese Application Publication No. 61-263917) and **Sugita *et al.*** (USP No. 6,723,732; Issued Apr. 20, 2004; 371 (c)(1), (2), (4) Date: Jul 19, 2001) in view of **Koide *et al.*** (Japanese Application Publication No. 10-265373) and **Akira *et al.*** (Japanese Application Publication No. 63-203613).

As discussed in the previous Office Action, Hiroyoshi *et al.* disclose the claimed active agent 3-methyl-1-phenyl-2-pyrazolin-5-one as a cerebral normalizing agent which has cerebral ischemia protecting action (Abstract). Referring now to the English translation of Hiroyoshi *et al.* provided by Applicants, the inventors disclose the use of 3-methyl-1-phenyl-2-pyrazolin-5-one as an active ingredient for cerebral normalization (page 1 of English translation). Thus, the use of the claimed compound to protect against cerebral dysfunction is not new or unobvious in view of the prior art. As Applicant's correctly observe in their response filed 6/5/2009, Hiroyoshi *et al.* do not teach percutaneous absorption of the active agent for protecting against cerebral dysfunction.

However, Sugita *et al.* disclose percutaneously administratable preparations containing cerebral function activators (Title; Abstract; col. 2, lines 3-7). In this regard, the inventors teach that orally administrable preparations generally lead to lack of sustained efficacy due to the extreme rise of blood concentration. The percutaneously administrable preparations of the invention overcome this problem and can reduce individual differences of blood concentration by avoiding the hepatic first-pass effect. Furthermore, percutaneously administrable preparations show continuous pharmacological efficacy because the plasma concentration of the active ingredient can be kept constant for a long duration by the sustained release to whole body circulation (col. 2, line 66 to col. 3, line 11). As such, percutaneous administration of cerebral protecting agents is likewise not new or unobvious in view of the prior art.

The instant claims, as amended, differ from Hiroyoshi *et al.* and Sugita *et al.* in that the primary and secondary references do not disclose the claimed excipients of the recited percutaneous absorption type pharmaceutical composition.

However, Koide *et al*., as discussed in the previous Office Action, disclose a tacky adhesive composition comprising a drug, water-soluble polymer, cross-linking agent a polyhydric alcohol and water (Abstract). The water soluble polymers include rubber polymers such as polyacrylates [0013], and these polymers make up 1- 15% [0014]. The formulation comprises crosslinking agents that make up from 0.1-10% of the formulation and include glycine [0017-0019]. The formulation comprises polyhydric alcohols such as ethylene glycol and propylene glycol that make up from 15-50% of the formulation [0020-0021]. The formulation further comprises tackifiers such as cellulosic resins, where the compounds are present in the formulation up to 15% [0020]. The water content of the formulation ranges from 40-70% [0038]. The drugs range from 0.001-10% of the drug formulation [0031]. The tacky formulation is applied to a film or substrate and applied to the skin [0022]. The tacky topical formulation, while disclosing a wide range of active agents is silent to the specific active agent of the instant claims.

Akira *et al*. disclose a hydrophilic percutaneous administration preparation containing a percutaneous absorption drug added to a base containing a water-soluble high polymer, a crosslinking agent, and a polyhydric alcohol (Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use percutaneous administration to administer the cerebral normalizing agent disclosed in Hiroyoshi *et al*. in light of the obvious benefits of such a mode of administration as disclosed in Sugita *et al*. The skilled artisan would expect that any cerebral normalizing agent would benefit from percutaneous administration in light of the teachings of Sugita *et al*. As such, Applicant's claimed method of administering a known cerebral normalizing agent using a known method of administering such compounds is not patentable over the cited prior art. It is noted that Sugita *et al*. disclose formulating active agent in an "aqueous base" as recited in the instant claims (col. 8, lines 59-62).

Claims 11 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Hiroyoshi *et al***. (Japanese Application Publication No. 61-263917) and **Sugita *et al***. (USP No. 6,723,732; Issued Apr. 20, 2004; 371 (c)(1), (2), (4) Date: Jul 19, 2001) in view of **Koide *et al***. (Japanese Application Publication No. 10-265373) and **Akira *et al***. (Japanese Application

Publication No. 63-203613), and further in view of **Mori *et al***. (EP 0 974 350 A1; Published 1/26/2000).

Hiroyoshi *et al*. disclose the claimed active agent 3-methyl-1-phenyl-2-pyrazolin-5-one as a cerebral normalizing agent which has cerebral ischemia protecting action (Abstract). Referring now to the English translation of Hiroyoshi *et al*. provided by Applicants, the inventors disclose the use of 3-methyl-1-phenyl-2-pyrazolin-5-one as an active ingredient for cerebral normalization (page 1 of English translation). Thus, the use of the claimed compound to protect against cerebral dysfunction is not new or unobvious in view of the prior art. As Applicant's correctly observe in their response filed 6/5/2009, Hiroyoshi *et al*. do not teach percutaneous absorption of the active agent for protecting against cerebral dysfunction.

However, Sugita *et al*. disclose percutaneously administratable preparations containing cerebral function activators (Title; Abstract; col. 2, lines 3-7). In this regard, the inventors teach that orally administrable preparations generally lead to lack of sustained efficacy due to the extreme rise of blood concentration. The percutaneously administrable preparations of the invention overcome this problem and can reduce individual differences of blood concentration by avoiding the hepatic first-pass effect. Furthermore, percutaneously administrable preparations show continuous pharmacological efficacy because the plasma concentration of the active ingredient can be kept constant for a long duration by the sustained release to whole body circulation (col. 2, line 66 to col. 3, line 11). As such, percutaneous administration of cerebral protecting agents is likewise not new or unobvious in view of the prior art.

The instant claims, as amended, differ from Hiroyoshi *et al*. and Sugita *et al*. in that the primary and secondary references do not disclose the claimed excipients of the recited percutaneous absorption type pharmaceutical composition.

However, Koide *et al*., as discussed in the previous Office Action, disclose a tacky adhesive composition comprising a drug, water-soluble polymer, cross-linking agent a polyhydric alcohol and water (Abstract). The water soluble polymers include rubber polymers such as polyacrylates [0013], and these polymers make up 1- 15% [0014]. The formulation comprises crosslinking agents that make up from 0.1-10% of the formulation and include glycine [0017-0019]. The formulation comprises polyhydric alcohols such as ethylene glycol and propylene glycol that make up from 15-50% of the formulation [0020-0021]. The formulation

further comprises tackifiers such as cellulosic resins, where the compounds are present in the formulation up to 15% [0020]. The water content of the formulation ranges from 40-70% [0038]. The drugs range from 0.001-10% of the drug formulation [0031]. The tacky formulation is applied to a film or substrate and applied to the skin [0022]. The tacky topical formulation, while disclosing a wide range of active agents is silent to the specific active agent of the instant claims.

Akira *et al*. disclose a hydrophilic percutaneous administration preparation containing a percutaneous absorption drug added to a base containing a water-soluble high polymer, a crosslinking agent, and a polyhydric alcohol (Abstract).

Mori *et al*. disclose formulations for percutaneous absorption of tranilast (Abstract). The external preparations are disclosed to be "excellent" in the release of active ingredient, to achieve a high percutaneous absoption, and to fully ensure effective drug concentration in the skin tissue and little irritation to the skin (*id*.). The percutaneous absorption composition of Mori *et al*. comprises an aqueous base containing the active agent, a solubilizer, a dispersant, an absorption aid, an adhesive and/or shape retaining agent, and water (*id*.; page 3, [0012]). Mori *et al*. disclose crotamiton and N-methyl-2-pyrrolidone as recited in claims 16 and 19 as dissolution mediums (page 3, [0016]); 1-menthol, crotamiton, and N-methyl-2-pyrrolidone as absorption aids (page 4, [0025]); tartaric acid as recited in claims 17-18 and 20 as a pH adjuster (page 4, [0026]); and 5 to 15% of water-soluble polymers such as sodium polyacrylate with aluminum hydroxide as a cross-linking agent (page 4, [0028]). Mori *et al*. further disclose use of polyhydric alcohols such as glycerol (*i.e*., glycerin) as adhesives and/or form-keeping agents in amounts of 5 to 40% by weight (page 5, [0030]). In Example 1 of Mori *et al*., the inventors teach preparation of a percutaneous absorption preparation that comprises:

i) 0.3% Active agent

ii) 2% Crotamiton

iii) 2.5% N-methyl-2-pyrrolidone

iv) 0.7% White carbon

v) 0.5% 1-menthol

vi) 0.25% Titanium dioxide

vii) 2.5% Tartaric acid

viii) 5% Sodium polyacrylate

ix) 6% Starch acrylate

x) 25% Glycerin

xi) 0.05% Aluminum hydroxide

xii) 52.7% Water

Mori *et al*. thus teach, suggest, and motivate percutaneous absorption preparations comprising the same excipients as recited in the instant claims.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use percutaneous administration to administer the cerebral normalizing agent disclosed in Hiroyoshi *et al*. in light of the obvious benefits of such a mode of administration as disclosed in Sugita *et al*. The skilled artisan would expect that any cerebral normalizing agent would benefit from percutaneous administration in light of the teachings of Sugita *et al*. As such, Applicant's claimed method of administering a known cerebral normalizing agent using a known method of administering such compounds is not patentable over the cited prior art. It is noted that Sugita *et al*. disclose formulating active agent in an "aqueous base" as recited in the instant claims (col. 8, lines 59-62) and Koide *et al*., Akira *et al*., and Mori *et al*. all teach percutaneous absorption compositions comprising the same excipients as recited in the instant claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Primary Examiner, Art Unit 1614

April 14, 2010